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Therapeutic Review
Intranasal Histamine H_1-receptor Antagonists (Antihistamines)

Overview/Summary

Azelastine hydrochloride is a histamine-1 (H_1)-receptor antagonist (antihistamine). By preventing the binding of histamine this, as well as the other agent in the class, olopatadine, prevent or delay smooth muscle contraction and nasal congestion.[1] It is metabolized by cytochrome P450 to desmethylazelastine, a major metabolite that also possesses H_1-receptor antagonist activity.[2-4] Although there is no difference in the pharmacology of the two branded azelastine hydrochloride products, there is a difference in their formulations. Astelin® nasal spray contains 0.1% azelastine hydrochloride in an aqueous solution (pH 6.8±0.3), benzalkonium chloride (125 µg/mL), edetate disodium, hypromellose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water. Astepro® nasal spray contains 0.1% azelastine hydrochloride in an isotonic aqueous solution, sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 µg/mL), and purified water (pH 6.4). The change in formulation is to minimize the potential for the adverse event of bitter taste that is associated with Astelin®.[2-4]

Olopatadine (Patanase®) is also an H_1-receptor antagonist. It is an intranasal spray that is indicated for the relief of seasonal allergic rhinitis (SAR) symptoms in patients age 12 years and older.[5] Symptoms of SAR includes runny nose, itchy nose, stuffy nose and sneezing.

Approximately 10% to 30% of Americans suffer from allergic rhinitis. Treatment options, in addition to avoiding known allergens, include intranasal corticosteroids, oral antihistamines, mast cell stabilizers and intranasal antihistamines. According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities, and pharmacological therapies. Intranasal corticosteroids should be considered first-line therapy in the majority of patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis.[6-7] Although antihistamines are considered an initial treatment option, intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious.[6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Azelastine hydrochloride (Astelin®, Astepro®)	Intranasal histamine-1 (H_1)-receptor antagonist (antihistamine)	-
Olopatadine hydrochloride (Patanase®)	Intranasal histamine H_1-receptor antagonist (antihistamine)	-

Indications

Table 2. Food and Drug Administration Approved Indications[2-5]

Generic Name	Indication
Azelastine	Astelin® is indicated for the treatment of seasonal allergic rhinitis (SAR) symptoms in adults and children 5 years and older; as well as for the treatment of vasomotor rhinitis symptoms in adults and children 12 years and older. Astepro® is indicated for the treatment of SAR symptoms in adults and children 12 years of age and older.

Generic Name	Indication
Olopatadine	Treatment of SAR symptoms in adults and children 12 years of age and older.

Pharmacokinetics

There is no significant difference in the pharmacokinetics of the two branded intranasal azelastine hydrochloride products.

Table 3. Pharmacokinetics[2-5]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Half-Life (hours)
Azelastine	40	Oxidation by cytochrome P450 system	Feces: 75	Yes; des-methyl-azelastine	Azelastine: 22 Des-methylazelastine: 52-54
Olopatadine	57	Not extensively metabolized	Urin:70; feces:17	6 minor metabolites	8-12

Clinical Trials

Overall, azelastine hydrochloride nasal spray has been found to be safe and efficacious in placebo controlled trials.[2-3,8-10] A meta-analysis of active comparators versus azelastine hydrochloride nasal spray in seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR) has been conducted.[10] In the meta analysis, comparators included beclomethasone nasal spray/loratadine, terfenadine, cetirizine, budesonide nasal spray, ebastine, levocabastine and loratadine. Although multiple analyses between azelastine hydrochloride and the comparators were conducted, a statistically significant difference in response was not identified.[10] A trial by Berger et al showed that azelastine hydrochloride nasal spray was significantly more efficacious than cetirizine in various symptom scores and a trial by Ratner et al showed that the combination of azelastine hydrochloride nasal spray and fluticasone nasal spray was significantly more efficacious than the individual agents in various symptom scores.[11-12] Comparable efficacy and safety between the two azelastine hydrochloride nasal spray's has also been reported.[2-3]

The efficacy and safety of olopatadine nasal spray has been examined in five randomized, double-blind, placebo-controlled trials assessing its effects in SAR.[13-17] Additionally, olopatadine was evaluated in a randomized, double-blind, placebo-controlled, parallel group trial of SAR patients comparing its effects to placebo and mometasone nasal spray.[18] Each of the five trials illustrated statistically significant improvement in Total Nasal Symptom Score (TNSS) scores compared to placebo. In a 2-week study by Meltzer et al[13] the average TNSS reduction was >35% compared to 27% for placebo treated patients. Ratner et al[14] reported a significant improvement in TNSS scores, with average treatment reductions exceeding 27% compared to 18% for placebo-treated patients. The treatment groups in the trial by Fairchild et al[15] had a statistically significant improvement in absolute and percent change from baseline TNSS scores compared to placebo. Similar TNSS score improvement was also observed by Hampel et al[16] when comparing olopatadine treatment with placebo. The Hampel et al. study also observed significant improvement in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores with olopatadine treatment compared to placebo.[16] A trial by Patel et al[17] observed statistically significant improvement in changes in TNSS score from baseline, with improvement occurring in 14 of the 16 measured time points. The trial by Patel et al[18] in which olopatadine was compared with nasal mometasone therapy and placebo, found significant differences in TNSS scores compared to placebo initially observed at 30 minutes after dosing olopatadine; contrasting with improvement observed after 150 minutes of mometasone dosing. Overall, olopatadine therapy was considered safe, with adverse events classified as mild and non-serious in nature.

Two trials have compared azelastine hydrochloride nasal spray and olopatadine nasal spray.[19-20] Pipkorn et al compared these agents in patients with SAR and found no significant difference between the agents in the reduction of sneezing, rhinorrhea, pruritus, congestion, posterior nasal drip and lysozome, albumin and histamine levels.[19] Meltzer et al compared these two agents and found that significantly more

patients favored/preferred olopatadine to azelastine.[20] Additionally olopatadine was found to be significantly more efficacious in a number of factors immediately post dose (smell, irritation etc).[20] However a number of these factors were no longer significant 45 minutes post dose.[20] No consistent clinically significant difference between azelastine hydrochloride nasal spray and olopatadine nasal spray has been documented.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lumry et al[8] Azelastine nasal spray, 1 spray per nostril twice daily (Astelin®) vs placebo, 1 spray per nostril twice daily	2 DB, PC, RCT Patients 12-75 years of age with moderate-to-severe SAR who were still symptomatic after 1 week placebo lead in period	N=554 2 weeks	Primary: Change from baseline in TNSS Secondary: Change from baseline to day 14 in individual symptoms, patient global evaluation and RQLQ, adverse events	Primary: In both studies the mean difference in TNSS was significantly different in favor of azelastine compared to placebo (2.69 vs 1.31; *P*=0.01 for study 1 and 3.68 vs 2.50; *P*=0.02 for study 2). Secondary: The mean percent improvement with azelastine was significantly better for itchy nose (*P*=0.02), runny nose (*P*=0.03) and sneezing (*P*<0.001), but not for nasal congestion (*P* value not reported) compared to placebo in study 1. The mean percent improvement with azelastine was significantly better for itchy nose (*P*=0.04), sneezing (*P*<0.02) and congestion (*P*=0.01), but not for runny nose (*P* value not reported) compared to placebo in study 2. A significantly greater number of patients rated their symptom improvement as better with azelastine compared to placebo in study 1 (67% vs 52%; *P*<0.001). A significantly greater number of patients rated their symptom improvement as better with azelastine compared to placebo in study 2 (74% vs 58%; *P*<0.01). The difference in the daily activity and nasal symptom domains of the RQLQ were significantly different in favor of azelastine vs placebo in both studies (*P*<0.05 for all). However the overall RQLQ was not significantly different between the two groups in study 1, but was in favor of azelastine in study 2 (*P*=0.02). In patients treated with azelastine, 8.3% reported a bitter taste and 0.4% reported somnolence. No other significant differences in adverse events were reported.
Meltzer et al[13] Olopatadine 0.4%, 2 sprays per nostril twice daily	DB, MC, PC, PG, RCT Patients, age 12 to 80 years of age, with SAR and	N=565 2 weeks	Primary: Percent change from baseline in reflective TNSS	Primary: Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in reflective TNSS as compared to placebo (*P*=0.004 and *P*<0.001 respectively). The average percent reductions were 35.8% and 39.2% respectively, compared to 27.0% for placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olopatadine 0.6%, 2 sprays per nostril twice daily vs placebo, 2 sprays per nostril twice daily	positive allergic sensitivity test		Secondary: Percent change from baseline in instantaneous TNSS, individual symptoms (runny nose, itching nose, sneezing, stuffy nose, watery eyes and itchy eyes), and RQLQ	Secondary: Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in instantaneous TNSS as compared to placebo (*P*=0.02 and *P*=0.003 respectively). The average percent reductions were 31.6% and 33.3% respectively, compared to 23.6% for placebo. Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in reflective and instantaneous evaluation of most symptoms as compared to placebo (reflective values: runny nose; *P*=0.046 and *P*=0.001 respectively, itchy nose; *P*=0.005 and *P*<0.001 respectively, sneezing; *P*<0.001 for both strengths). Reflective and instantaneous scores for severity of stuffy nose were not significantly improved (reflective values for both strengths; *P*=0.70 and *P*=0.85). The quality of life scores for both treatment strengths were significantly improved from baseline and greater than placebo (*P*=0.02 and *P*<0.001 for respective strengths compared to placebo). The 0.6% strength score improved in all 7 domains, while the 0.4% improved in 4 of the 7 domains.
Ratner et al[14] Olopatadine 0.4%, 2 sprays per nostril twice daily vs olopatadine 0.6%, 2 sprays per nostril twice daily vs placebo, 2 sprays per nostril twice daily	DB, MC, PC, PG, RCT Patients, age 12 to 80 years of age, with SAR and positive allergic sensitivity test	N=675 2 weeks	Primary: Percent change from baseline in reflective TNSS Secondary: Percent change from baseline in instantaneous TNSS, individual symptoms (runny nose, itching nose, sneezing, stuffy nose, watery eyes and itchy eyes), and	Primary: Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in reflective TNSS as compared to placebo (*P*<0.001 for both). The average percent reductions were 27.6% and 30.1% respectively, compared to 18.7% for placebo. Secondary: Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in instantaneous TNSS as compared to placebo (*P*<0.001 and *P*=0.002 respectively). The average percent reductions were 24.3% and 26.2% respectively, compared to 15.8% for placebo. Treatment with 0.4% and 0.6% olopatadine resulted in significant improvement in reflective and instantaneous evaluation of most symptoms as compared to placebo (reflective values: runny nose; *P*<0.001 for 0.6% only, itchy nose and sneezing; *P*<0.001 for both strengths and symptoms, itchy eyes; *P*<0.001 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			safety	*P*=0.008, watery eyes: *P*=0.002 and *P*=0.009). Adverse events were not considered serious. Bitter taste was the most common adverse event and somnolence occurred in 0.4% and 1.3% of the 0.6% and 0.4% olopatadine treatment groups respectively. No changes in laboratory results were seen.
Fairchild et al[15] Olopatadine 0.4%, 2 sprays per nostril twice daily vs olopatadine 0.6%, 2 sprays per nostril twice daily vs placebo, 2 sprays per nostril twice daily	DB, MC, PC, RCT Patients, 12 years and older, with a 2 year history of SAR and positive skin test to relevant pollen	N=1,233 2 weeks	Primary: TNSS change from baseline Secondary: Safety, RQLQ, and WPAI-AS	Primary: Reflective TNSS absolute and percent change from baseline was significantly greater for both treatment groups compared to placebo (*P*<0.0001 for both, with decrease of 3.1 [-34.0%] for 0.6% and of 2.9 [-31.3%] for 0.4%, compared to placebo 2.1 [-22.5%]). Secondary: The most commonly reported adverse events were unpleasant taste and headache. Dysgeusia was reported more frequently in the 0.6% and 0.4% strengths than placebo (13.0% and 7.4% compared to 0.5% respectively). RQLQ score improved significantly in both treatment groups compared to placebo (*P*<0.0001 and *P*=0.0002). Changes in RQLQ scores correlate with changes in TNSS (*P*<0.001). WPAI-AS scores on work impairment (*P*=0.0009 and *P*=0.0198) and activity impairment (*P*=0.0027 and *P*=0.0400) improved significantly in both treatment groups compared to placebo, but not in classroom impairment (*P* value not significant). Changes in WPAI-AS scores for work impairment improvement and activity impairment improvement correlate with changes in TNSS (*P*<0.001 for both).
Hampel et al[16] Olopatadine 0.4%, 2 sprays per nostril twice daily vs olopatadine 0.6%, 2	DB, MC, RCT Patients, 12 years old and older, with 2 year history of SAR and positive skin allergy test	N=675 2 weeks	Primary: RQLQ Secondary: TNSS	Primary: Both treatments resulted in significant improvement in RQLQ (score change from baseline 1.1 for both treatments) as compared to placebo (score change from baseline 0.8; *P*<0.01). The treatment strengths were not different from each other in RQLQ. The improvement in RQLQ is considered clinically significant as it correlates with TNSS scores.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sprays per nostril twice daily vs placebo, 2 sprays per nostril twice daily				Secondary: TNSS score improved for both treatment strengths as compared to placebo. The treatment strengths were not different from each other in RQLQ scores *(P* values not reported).
Patel et al[17] Olopatadine 0.2%, 2 sprays/nostril vs olopatadine 0.4%, 2 sprays/nostril vs olopatadine 0.6%, 2 sprays/nostril vs placebo, 2 sprays/nostril	DB, PC, PG, RCT, single dose Patients, 17 to 65 years old, with a history of SAR during the fall season and allergic to short ragweed pollen; patients were exposed to pollen in an environmental exposure chamber and had to achieved a TNSS score of at least 6 of 12 to receive medication	N=320 12 hours	Primary: TNSS change from baseline Secondary: Patient global rating scale (7 unit scale: 0=very much better, 6=very much worse), individual symptoms, and safety	Primary: Treatment resulted in significant change in TNSS score from baseline at the first time point of 30 minutes until the last at 11.5 hours (*P*<0.05 for all strengths compared to placebo). 0.4% and 0.6% achieved significant improvement compared to placebo at 14 of 16 time points; 0.2% achieved significance at 12 of the 16 time points. 0.6% achieved maximum decrease in TNSS sooner than other strengths (*P* value not given). Secondary: 0.4% and 0.6% treatments were significantly better than placebo in the number of patients rating symptoms as very much and moderately better. Patients reported significant improvement in runny nose and itchy nose for the following: 0.2% at 4 and 5 time points respectively, 0.4% at 8 and 2 time points respectively, 0.6% at 12 and 8 time points respectively. All treatments resulted in significant improvement over placebo in sneezing at all time points. All treatments achieved significant improvement over placebo at 90 minutes (*P* value not reported). Adverse events occurring during treatment were determined to be non-serious.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lee et al[10] Azelastine nasal spray vs placebo or active comparators (budesonide nasal spray, certrizine, ebastine*, levocabastine*, loratadine, terfenadine*, and the combination of beclomethasone nasal spray and loratadine)	MA Patients 12 years of age and older diagnosed with allergic rhinitis or nonallergic vasomotor rhinitis	N=2,906 34 trials/data points ranging in duration from 2 days to 8 weeks	Primary: NNT, TNSS Secondary: Not reported	Primary: For azelastine compared to placebo the point estimates for the risk difference were positive ranging from 0.05 (95% CI, -0.08 to 0.17) to 0.33 (95% CI, 0.16 to 0.50). This resulted in NNT's ranging from 3.0-20.0 and a summary NNT of 5.0 (95% CI, 3.3-10.0). Results for heterogeneity of the azelastine vs placebo trials was significant (*P*=0.054). For azelastine compared to active comparators the point estimate for the risk difference was 0.015 (95% CI, -0.044 to 0.073). This resulted in a point estimate for the NNT of 66.7, which was not significantly different between azelastine and the comparators. Results for heterogeneity of the azelastine vs comparator trials was significant (*P*=0.006). For TNSS azelastine was more efficacious compared to placebo (effect size, 0.36; 95% CI, 0.26 to 0.46). Secondary: Not reported
Ghimire[9] Azelastine nasal spray (Group A) vs beclomethasone nasal spray (Group B) vs placebo nasal spray (Group C)	CC, PRO, R Patients with a history allergic rhinitis who were symptomatic	N=75 4 weeks	Primary: TSC, individual symptom score Secondary: Adverse events	Primary: In group A and B the TSC was reduced by 84.0% compared to 38.0% in group C. In group A and B the mean score for sneezing was reduced by 95.0% compared to 28.3% in group C. In group A and B the mean score for rhinorrhea was reduced by 94.4% and 95.3% compared to 25.0% in group C. Group B was the only one to reduce stuffiness significantly (95.0%). Secondary: No significant adverse events were observed in the treatment groups.
Patel et al[18] Olopatadine 0.6%, 2 sprays per nostril	DB, PC, PG, RCT, single dose, environmental exposure study	N=425 12 hours	Primary: TNSS change from baseline	Primary: Olopatadine treatment resulted in a significant change in TNSS from baseline, at all 16 time points, between 0 and 720 minutes, compared to placebo (*P*<0.05) and at all time points between 60 and 600 minutes after dose when

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 50 µg nasal spray vs placebo	Patients, age 18 years and older, with moderate to severe SAR and sensitivity to ragweed		Secondary: Patient global rating scale (7 unit scale: 0=very much better, 6=very much worse) and individual symptoms	compared to mometasone (P<0.05). Significant differences in TNSS compared to placebo were first seen at 30 minutes after olopatadine dose, compared to 150 minutes after mometasone dose. Secondary: Patients reported improvement in allergy symptoms significantly more often in the olopatadine group than the placebo and the mometasone group at 4 hours: olopatadine–88.0%, compared to placebo–59.3%, and mometasone–73.9% and at 12 hours: olopatadine–62.7%, compared to placebo–29.8%, and mometasone–50.7% (P<0.05 for all). Olopatadine treatment resulted in significant improvement in symptom scores compared to placebo for the following: sneezing, runny, itchy and stuffy nose and compared to mometasone: runny nose, itchy nose and stuffy nose at >60% of the time points.
Pipkorn et al[19] Study 1, phase 1: Olopatadine 0.1% nasal spray vs placebo Study 1, phase 2: olopatadine 0.2% nasal spray vs placebo	2 DB, R, XO Patients 20-64 years of age free of symptoms at time of study enrollment, in good physical condition, taking no medications, and documented symptoms of SAR confirmed by skin test to ragweed or Timothy grass	Study 1, phase 1: N=16 Study 1, phase 2: N=19 Study 2: N=18 Duration was not specified	Primary: Number of sneezes after each dose and levels of mediators (albumin, and lysozyme) Secondary: VAS scores for rhinorrhea, nasal pruritus, nasal congestion, and posterior nasal drainage, histamine levels	Primary: Study 1, phase 1: Compared to placebo, pretreatment with olopatadine significantly reduced sneezing (P=0.008). There was a significant difference in favor of the treatment group in lysozyme but not in albumin level. Study 1, phase 2: Compared to placebo, pretreatment with olopatadine significantly reduced sneezing (P=0.002). There was a significant difference in favor of the treatment group in lysozyme and albumin level. Study 2: There was no significant difference between the two groups in reduced sneezing (P=0.33). There was no significant difference in between the two groups in lysozyme (P=0.12) and albumin level (P=0.88). Secondary: Study 1, phase 1: Compared to placebo, pretreatment with olopatadine significantly reduced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study 2: azelastine nasal spray (Astelin®) vs olopatadine 0.1% nasal spray				rhinorrhea (*P*<0.001), pruritus (*P*<0.001), congestion (*P*=0.002), and posterior nasal drip (*P*=0.03). There was no significant difference in histamine level. Study 1, phase 2: Compared to placebo, pretreatment with olopatadine significantly reduced rhinorrhea (*P*=0.048), pruritus (*P*=0.01), congestion (*P*=0.01), and posterior nasal drip (*P*=0.005). There was a significant difference in histamine level in the treatment group. Study 2: There was no significant difference between the two groups in the reduction of rhinorrhea (*P*=0.12), pruritus (*P*=0.37), congestion (*P*=0.98), posterior nasal drip (*P*=0.98) and histamine level (*P*=0.83).
Meltzer et al[20] Azelastine nasal spray (Astelin®) vs olopatadine nasal spray Patients recieved one administration of each treatment consisting of two sprays in each nostril. Each medication was seperated by a 24 hour washout period.	DB, MC, R, XO Patients ≥18 years of age with at least a 2 years history of SAR or PAR symptomatic at the time of enrollment	N=110 4-17 days (depending on patient specific washout period)	Primary: Mean patient preference and overall aftertaste Secondary: Sensory attribute of taste perception, overall product preference, likelihood of use over extended time, perceptions of smell and nasal irritation, sensation of medication dripping out of nose/down throat, moistness of nose and throat, overall satisfaction	Primary: Overall 60.6% of patients favored olopatadine, 30.3% favored azelastine and 90.2% had no preference (*P*=0.0005). Mean patient preference was significantly greater with olopatadine than azelastine for overall aftertaste (*P*=0.0005), overall preference (*P*=0.0001), and likelihood of use (*P*=0.0004). Secondary: Mean patient satisfaction scores for immediate taste were significantly better with olopatadine compared to azelastine (*P*=0.0001), but there was no significant difference in 45 minute after taste (*P* not reported). Immediately post dose mean satisfaction was significantly greater for olopatadine vs azelastine in smell, nasal congestion, urge to sneeze, dripping down nose, dripping down throat, and overall satisfaction (*P*≤0.0146). There was no significant difference in moistness of nose or throat. Forty-five minutes post dose mean satisfaction was significantly greater for olopatadine than azelastine in nasal irritation, urge to sneeze and overall satisfaction (*P*≤0.0487). There was no significant difference in smell, dripping down nose, dripping down throat, and moistness of nose or throat. No significant differences in adverse events were reported in the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Berger et al[11] Azelastine nasal spray, 2 sprays per nostril twice daily (Astelin®) vs cetirizine 10 mg tablets by mouth once daily	DB, MC, R Patients 12 years of age and older with moderate-to-sever SAR	N=360 2 weeks	Primary: TNSS Secondary: RQLQ, individual symptoms, safety	Primary: Compared with the baseline score the combined morning and evening 12-hour reflective TNSS was significantly improved in both treatment groups (*P*<0.001). The mean improvement from baseline TNSS in the ITT population was 4.6±4.2 in the azelastine group compared to 3.9±4.3 in the cetirizine group (*P*=0.14), correlating to a percent change of 23.9% and 19.6% in the azelastine and cetirizine groups, respectively (*P*=0.08). The mean improvement from baseline TNSS in the evaluable population was 4.6±4.2 in the azelastine group compared to 3.8±4.3 in the cetirizine group (*P*=0.09), correlating to a percent change of 24.2% and 19.2% in the azelastine and cetirizine groups, respectively (*P*=0.046). Secondary: Compared with the baseline score the each individual RQLQ domain score and the overall RQLQ score was significantly improved in both treatment groups (*P*<0.001). Compared with cetirizine, azelastine significantly improved each domain of the RQLQ (*P*≤0.05) and the overall RQLQ score (*P*=0.002). For the 4 symptoms of the TNSS, compared with cetirizine, azelastine significantly improved nasal congestion (*P*=0.49) and sneezing (*P*=0.01) to a greater extent. However there was no significant difference in improvement in itchy nose and runny nose. Bitter taste was the common adverse event with azelastine. No other significant difference was noted in adverse events.
Ratner et al[12] Azelastine nasal spray, 2 sprays per nostril twice daily (Astelin®) and placebo nasal	DB, DD, MC, PG, R Patients 12 years and older with a minimum 2-year	N=151 2 weeks	Primary: Change from baseline in TNSS Secondary: Change from	Primary: Compared to baseline all three treatment groups significantly improved TNSS (*P*<0.001). In the azelastine, fluticasone and combination groups the mean improvement from baseline TNSS was 4.8±4.3, 5.2±4.6, and 7.4±5.6, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
spray once in the morning vs fluticasone nasal spray, 2 sprays per nostril once daily in the morning and placebo nasal spray twice daily vs azelastine nasal spray, 2 sprays per nostril twice daily (Astelin®) and fluticasone nasal spray, 2 sprays per nostril once daily in the morning	history of allergy to Texas mountain cedar confirmed in the past year by positive skin test		baseline for each individual treatment day, change from baseline for each individual symptom score, change from baseline in the RQLQ, safety	The improvement from baseline TNSS was 27.1% with fluticasone, 24.8 with azelastine, and 37.9% with the combination (*P*<0.05 for the combination vs either agent alone). Compared to the azelastine and fluticasone there were absolute improvements of 11.0% (*P*=0.007) and 13.0% (*P*=0.02) with the combination, respectively. Secondary: Compared to either single treatment the combination was significantly more efficacious in treating the symptoms of congestion and itchy nose (*P*<0.05). Compared to fluticasone the combination was significantly more efficacious in treating the symptom of runny nose (*P*<0.05). Compared to azelastine the combination was significantly more efficacious in treating the symptom of sneezing (*P*<0.05). On study days 3-14 the combination was significantly more efficacious than azelastine alone (*P*<0.05). On study days 4 and 6-11 the combination was significantly more efficacious than fluticasone alone (*P*<0.05). Compared to baseline all three treatments significantly improved overall RQLQ as well as the individual domains of RQLQ (*P*<0.01).In the overall RQLQ score the mean change from baseline was greater for the combination (1.92) compared to azelastine (1.21) and fluticasone (1.40). The difference was significant compared with azelastine but not fluticasone. Bitter taste was the most common adverse event with azelastine (8.2% vs 2.0% in the fluticasone group and 13.5% in the combination group). In 4.1% of the azelastine group, 4.0% of the fluticasone group and 5.8% of the combination group headache was reported.

* Agent not available in the United States.
Study abbreviations: CC=case control, DB=double-blinded, DD=double dummy, MA=meta analysis, MC=multicenter, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, XO=cross over
Miscellaneous abbreviations: CI=confidence interval, ITT=intent to treat, NNT=number needed to treat, PAR=perennial allergic rhinitis, RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire, SAR=seasonal allergic rhinitis, TNSS=Total Nasal Symptom Score, TSC=total symptom complex score, VAS=visual analog scale, WPAI-AS=Work Productivity and Activity Impairment Questionnaire-Allergy Specific

Special Populations

Table 5. Special Populations[2-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Azelastine	Astelin® is not approved in children <5 years of age. Astepro® is not approved in children <12 years of age. No dose adjustment required for elderly.	No dose adjustment necessary.	No dose adjustment necessary.	C	Unknown
Olopatadine	Not approved in children <12 years of age. Lack of clinical data in patient's ≥65 years old precludes the ability to establish any differences in response between elderly and young patients.	No dose adjustment necessary.	No dose adjustment necessary.	C	Unknown

Adverse Drug Events

The following table lists the most commonly reported adverse events associated with Astelin® nasal spray. Results are pooled from trials comparing the product to placebo for both Food and Drug Administration approved indications at a dose of 2 sprays in each nostril twice daily.[2] Additionally two, placebo controlled trials (N=276) evaluating Astelin® nasal spray at a dose of 1 sprays in each nostril twice daily for the treatment of seasonal allergic rhinitis reported lower rates of bitter taste (8.3% for Astelin® nasal spray, 0.0% for placebo) and somnolence (0.4% for Astelin® nasal spray, 0.0% for placebo) than those seen in the 2 sprays in each nostril twice daily studies.[2]

Table 6. Adverse Drug Events (%)[2]

	Reported Frequency (%)	
Adverse Event	Astelin® (2 Sprays Twice Daily) N=607	Placebo N=563
Bitter taste	19.4 to 19.7	0.6 to 2.4
Headache	7.9 to 14.8	7.6 to 12.7
Somnolence	3.2 to 11.5	1.0 to 5.4

The following table lists the most commonly reported adverse events associated with Astepro® nasal spray. Adverse events were reported by patients who were randomized to one of six treatments for seasonal allergic rhinitis.[3]

Table 7. Adverse Drug Events (%)[3]

Adverse Event	Reported Frequency (%)					
	1 Spray Twice Daily			2 Sprays Twice Daily		
	Astepro® N=139	Astelin® N=137	Placebo N=137	Astepro® N=146	Astelin® N=137	Placebo N=138
Bitter taste	8 (6)	13 (10)	2 (2)	10 (7)	11 (8)	3 (2)
Headache	2 (1)	5 (4)	1 (<1)	4 (3)	3 (2)	1 (<1)
Somnolence	2 (1)	2 (2)	0 (0)	3 (2)	2 (1)	0 (0)

The following table lists the most commonly reported (≥0.9% incidence) adverse events with olopatadine nasal spray.[5] The adverse events were documented during clinical trials involving patients 12 years of age and older, with seasonal or perennial allergic rhinitis.[5] Overall there were no differences in the reported incidences of adverse events based upon gender or age.[5]

Table 8. Adverse Drug Events (%)[5]

Adverse Drug	Reported Frequency (%)	
	Olopatadine (N=587)	Placebo (N=593)
Bitter taste	75 (12.8)	5 (0.8)
Cough	8 (1.4)	3 (0.5)
Creatine phosphokinase elevation	5 (0.9)	2 (0.3)
Dry mouth	5 (0.9)	1 (0.2)
Epistaxis	19 (3.2)	10 (1.7)
Fatigue	5 (0.9)	4 (0.7)
Headache	26 (4.4)	24 (4.0)
Influenza	5 (0.9)	1 (0.2)
Nasopharyngitis	5 (0.9)	4 (0.7)
Pharyngolaryngeal pain	13 (2.2)	8 (1.3)
Post-nasal drip	9 (1.5)	5 (0.8)
Somnolence	5 (0.9)	2 (0.3)
Throat irritation	5 (0.9)	0 (0.0)
Urinary tract infection	7 (1.2)	3 (0.5)

Contraindications/Warnings/Precautions

Azelastine hydrochloride may cause drowsiness, and somnolence has been reported. As such, the concurrent use of azelastine hydrochloride with alcohol or other central nervous system depressants should be avoided.[2-4] Additionally the safety and efficacy of Astelin® has not been established in children below 5 years of age.

Epistaxis and nasal ulceration have been reported in olopatadine nasal spray clinical trials. Nasal septal perforation has occurred with a different formulation of olopatadine (povidone-containing) nasal spray (not commercially available). No reports of nasal septal perforation have been reported with Patanase®.[4-5] Patients should be cautioned that somnolence may occur with olopatadine. If present, activities requiring mental alertness, as well as concomitant use of alcohol and other central nervous system depressants known to cause somnolence, should be avoided while using olopatadine.[4-5]

These agents are contraindicated in patients with a known hypersensitivity to any component of the nasal spray.[2-5]

Drug Interactions

There are no significant drug interactions reported with the use of the intranasal formulation of azelastine hydrochloride.[2-4] Drug interaction studies were not performed with olopatadine nasal spray. Drug interactions are not anticipated due to lack of inhibition or induction of CYP450 hepatic enzymes. Drug displacement when co-administered with drugs having high protein binding is not anticipated due to the relatively modest plasma protein binding of olopatadine.[4-5]

Dosage and Administration

Table 9. Dosing and Administration[2-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Azelastine	Seasonal allergic rhinitis: 12 years of age and older, 1-2 sprays in each nostril twice	Seasonal allergic rhinitis: 5 to 11 years of age, 1 spray in each nostril twice daily	Nasal spray: 137 µg/spray (200 metered doses per

Generic Name	Adult Dose	Pediatric Dose	Availability
	daily (Astelin® nasal spray and Astepro® nasal spray) Vasomotor rhinitis: 2 sprays in each nostril daily (Astelin® nasal spray)	(Astelin® nasal spray) Vasomotor rhinitis: Safety and efficacy in children <12 years of age have not been established. (Astelin® nasal spray and Astepro® nasal spray).	unit)
Olopatadine	Seasonal allergic rhinitis: 12 years of age and older, 2 sprays in each nostril twice daily	Safety and efficacy in children <12 years of age have not been established.	Nasal spray: 665 µg/spray (240 metered doses per unit)

Clinical Guidelines

According to the current clinical guidelines on the management of rhinitis, treatment should consist of patient education, allergen avoidance activities, and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants, whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms. Intranasal corticosteroids should be considered first-line therapy in patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis.[6-7] Antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids. The newer second-generation antihistamines are recommended due to the reduced potential for sedation and central nervous system impairment and cromolyn is more effective when used prior to the onset of allergic symptoms.[7] The combination of an antihistamine and a leukotriene inhibitor is more effective than either therapy alone, however, the combination is not more efficacious than treatment with intranasal corticosteroids.[6] Intranasal anticholinergics have increased efficacy for the management of rhinorrhea when used in combination with intranasal corticosteroids. Topical decongestants should only be used for the short-term management of nasal congestion due to the potential to induce rebound congestion. Other therapies for the management of rhinitis include oral corticosteroids and immunotherapy. Both of these treatment options should be reserved for those patients with severe refractory rhinitis.

Table 10. Clinical Guidelines

Clinical Guidelines	Recommendations
Joint Task Force on Practice Parameters for Allergy and Immunology: **The Diagnosis and Management of Rhinitis: An Updated Practice Parameter (2008)**[6]	Diagnosis • An effective evaluation of a patient with rhinitis includes a determination of the pattern, chronicity, and seasonality of nasal and related symptoms; response to medications; presence of coexisting conditions; occupational exposure; and a detailed environmental history and identification of precipitating factors. • A physical examination with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. • Skin testing is the preferred test for the diagnosis of IgE-mediated sensitivity and is indicated to provide evidence of allergic basis for the causes of the patient's symptoms. • Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis but may be useful when the diagnosis of allergic rhinitis is in question. • The measurement of total IgE should not be routinely performed. • Cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis are not recommended diagnostic procedures.

Clinical Guidelines	Recommendations
	Treatment • The management and monitoring of rhinitis should be individualized and based on symptoms, physical examination findings, comorbidities, patient age and patient preferences. • Environmental control measures include avoidance of known allergic triggers when possible. • The available second-generation oral antihistamines, which are generally preferred over first-generation antihistamines, appear to be equally effective in the treatment of allergic rhinitis. • Concerning the second generation antihistamines, fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. • Intranasal antihistamines are efficacious and equal to or superior to oral second-generation antihistamines for treatment of seasonal allergic rhinitis. • Intranasal antihistamines may be considered for use as first-line treatment for the treatment of allergic and nonallergic rhinitis. • Leukotriene receptor antagonists alone or in combination with antihistamines are effective in the treatment of allergic rhinitis. • Topical decongestants are not recommended for regular daily use but can be considered for short-term management of nasal congestion. • Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis and all are considered equally efficacious. • Intranasal corticosteroids can provide significant relief of symptoms when used on a regular basis as well as an as-needed basis. • Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. • A short course of oral corticosteroids may be appropriate for very severe or intractable nasal symptoms or significant nasal polyposis. • Intranasal cromolyn sodium may be effective for the prevention and treatment of allergic rhinitis. • Intranasal anticholinergics may be effective in reducing rhinorrhea and are more effective when used in combination with intranasal corticosteroids. • Allergen immunotherapy is effective and should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. • Surgery may be indicated in the management rhinitis.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults (2008)**[7]	Diagnosis • Patients can present with any of the following symptoms: congestion, rhinorrhea, pruritus, sneezing, posterior nasal discharge, and sinus pressure/pain. • A past medical history of facial trauma or surgery, asthma, rhinitis, atopic dermatitis, or thyroid disease may be suggestive of a rhinitis. In addition, a family history of atopy or other allergy associated conditions make allergic rhinitis more likely. • The most common physical findings suggestive of rhinitis tend to be swollen nasal turbinates, rhinorrhea and pruritus however allergic conjunctivitis may also be present.

Clinical Guidelines	Recommendations
	• Symptoms suggestive of allergic or episodic rhinitis include sneezing, itching of the nose, palate or eyes, and clear rhinorrhea. Nasal congestion is more commonly associated with perennial rhinitis. • Diagnostic testing should be considered if the results would change management. • Skin tests and radioallergosorbent tests identify the presence of IgE antibody to a specific allergen and are used to differentiate allergic from nonallergic rhinitis and to identify specific allergens causing allergic rhinitis. • A nasal smear for eosinophils can not differentiate allergic from nonallergic rhinitis. The test is a good predictor of a patient's response to treatment topical nasal corticosteroids. • Peripheral blood eosinophil count, total serum IgE level, Rinkel method of skin titration and sublingual provocation testing are not recommended. Treatment • If a clinical diagnosis is obvious, symptomatic treatment, which consists of education on avoidance and medication therapy, should be initiated. • Avoidance of triggers is recommended. • Intranasal corticosteroids are the most effective single agents for controlling the spectrum of allergic rhinitis symptoms and should be considered first-line therapy in patients with moderate to severe symptoms. • Regular daily use of intranasal corticosteroids is required to achieve optimal results. • Systemic corticosteroids should be reserved for refractory or severe cases of rhinitis. Injectable steroids are not generally recommended. • Antihistamines are effective at controlling all symptoms associated with allergic rhinitis except nasal congestion. • Antihistamines are somewhat less effective than intranasal corticosteroids however oral antihistamines are an effective alternative in patients who cannot use or prefer not to use intranasal corticosteroids. They also can be added as adjunctive therapy to intranasal corticosteroids. • Second-generation antihistamines are recommended because they are less sedating and cause less central nervous system impairment. • Leukotriene inhibitors are as effective as second-generation antihistamines for the treatment of allergic rhinitis however are not as effective as intranasal corticosteroids. • Oral decongestants are effective in reducing nasal congestion. • Topical decongestants, which have the potential to induce rebound congestion after 3 days, are effective for the short-term relief of nasal congestion. • Cromolyn is most effective when used prior to the onset of allergic symptoms and is a good alternative to corticosteroids however four times daily dosing may cause compliance problems. • Intranasal anticholinergics are effective in relieving anterior rhinorrhea in allergic and nonallergic rhinitis. • Reserve immunotherapy for patients with significant allergic rhinitis in which avoidance activities and pharmacotherapy are insufficient to control symptoms. • If adequate relief is achieved appropriate follow-up should include further

Clinical Guidelines	Recommendations
	education on avoidance activities and medications. • If patients anticipate unavoidable exposure to known allergens they should begin the use of medications prior to exposure. • If adequate relief is not achieved within 2 to 4 weeks consider a trial of another medication, allergen skin testing by a qualified physician, a complete nasal examination, or a diagnosis of nonallergic rhinitis. • Treatment options for nonallergic rhinitis include intranasal corticosteroids, oral decongestants and antihistamines, topical antihistamines, and nasal strips.

Conclusions

Azelastine hydrochloride is an intranasal antihistamine that is available as two different branded agents (Astelin® and Astepro®), that are not interchangeable. Astelin® is Food and Drug Administration (FDA) approved for the treatment of seasonal allergic rhinitis (SAR) and nonallergic vasomotor rhinitis. Astepro® is currently FDA approved for the treatment of SAR; however, it has not yet been studied in nonallergic vasomotor rhinitis. They differ in their formulation as Astepro® contains sorbitol and sucralose to potentially decrease the incidence of bitter taste associated with Astelin®.[2-4] There are no other significant differences between the two branded azelastine hydrochloride nasal sprays. Olopatadine is also an intranasal antihistamine that is a treatment option for the management of SAR.

Clinical trials have demonstrated that these agents are more effective than placebo and as effective as other alternatives in treating the symptoms of SAR.[8-20] Studies have also demonstrated that Astelin® is effective in the treatment of nonallergic vasomotor rhinitis.[2-3,8-12] Two published trials have compared azelastine hydrochloride nasal spray and olopatadine nasal spray with varying results.[19-20]

Consensus guidelines offer multiple treatment options and do not offer a precise step-therapy approach for treating allergic rhinitis. Although many drug classes are available for the treatment of allergic rhinitis, intranasal corticosteroids are the most effective agents in the treatment of symptoms.[6-7] Oral antihistamines are also an effective treatment option and all antihistamines appear to be equally effective, while the second-generation agents have a more favorable side effect profile.[6-7] For both allergic and nonallergic rhinitis, intranasal antihistamines may be considered a first line treatment option.

Recommendations

In recognition that the safety and efficacy profile of these agents is comparable to other agents routinely used for the treatment of seasonal allergic rhinitis symptoms and/or vasomotor rhinitis symptoms, and that they lack a unique advantage over the other alternatives as well as cost considerations, no changes are recommended to the current approval criteria.

Intranasal antihistamines (Astelin®, Astepro®, Patanase®) require prior authorization with the following approval criteria:

- The diagnosis or indication for the requested medication is allergic rhinitis.

AND

- The patient has had a documented side effect, allergy, or treatment failure to loratadine (OTC) **OR** cetirizine (OTC) **AND** a preferred nasal glucocorticoid.

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